Development of a Novel Risk Prediction Model for Cisplatin Nephrotoxicity

Introduction

The grant proposal included in this document aims to satisfy the written thesis defense requirement for the Masters' Program in Clinical and Translational Investigation. This grant aims to bring Nephrology expertise to the practice of selecting candidates for cisplatin chemotherapy in order to develop novel strategies with the goal of reducing nephrotoxicity. Our hope is that if successful, this would reduce the burden of kidney disease (acute kidney injury and chronic kidney disease) amongst patients receiving cisplatin chemotherapy. An oral thesis defense titled "Incidence, Trends and Predictors of Cisplatin Nephrotoxicity" was presented using the same database on April 20, 2016.

Project Summary/Abstract

Cisplatin is a chemotherapy drug that will be used to treat approximately 850,000 new cancer patients in 2015. Despite decades of its use, toxicity to the kidney remains a problem in 25-30% of the patients. Given the high frequency of kidney toxicity, we see as Nephrologists, a need to readdress methods for evaluating candidacy for cisplatin use in Oncology. Through this project, we may change the paradigm of selecting candidates and evaluating risk of cisplatin chemotherapy, which is an essential step prior to offering this drug as an option to patients. We propose to challenge the current method used for estimating kidney function, which is using serum creatinine or estimated creatinine clearance by the Cockcroft-Gault equation. Our first aim is to compare the estimated glomerular filtration rate (eGFR) equation by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for determining eligibility to receive cisplatin, since it is the most accurate equation available for estimating kidney function at the present time. Our second aim is to derive a risk prediction model using readily available clinical and laboratory variables that would enable clinicians to instantly compute the risk of kidney toxicity during the office visit and arrive at a graded score. This score could then be presented to patients as a low-, medium- or high-risk measure to further inform their decision-making regarding the treatment and to jointly (with their physicians) make an informed choice in the context of other options available. We propose to achieve the above aims by analyzing a large group of over 6000 patients that we have assembled using the Research Patient Data Repository (RPDR) and Oncology Data Retrieval System (OncDRS), which are large data repositories of patients treated at Partners affiliated hospitals and Dana Farber Cancer Institute, respectively. Detailed information collected from these patients who have been treated with cisplatin over the past 15 years includes demographics, chemotherapy, other medications, medical history and laboratory values. By performing sophisticated statistical analysis on these data, we will be able to understand the strength of these associations and thus identify major risk factors causing kidney toxicity. The model will be developed from the larger of the two group of patients treated at one hospital (derivation cohort) and testing our findings on the second group (validation cohort). We expect the results from this study to influence clinical practice and have lasting, positive short- and long-term impact on the overall health of patients receiving this drug; as well as identifying and redirecting patients with heightened risk of toxicity. If successful, ours will be the largest study on this topic and offer a novel method to address an old problem.

Specific Aims

Cisplatin is an alkylating anti-neoplastic agent that will be used as a first or second line treatment for an estimated 850,000 new cancers in 2015 in the United States. It was first introduced into clinical practice in 1978 and since then has led to greater than 90% cure of testicular cancer and helped save lives of millions of patients with bladder, cervical, ovarian, lung, gastric, breast, head and neck cancers, malignant mesothelioma and some less-common tumors. Despite a rapid rate of introduction of novel chemotherapeutics in oncology, this drug remains the backbone of several chemotherapy regimens now five decades since its discovery. Two essential issues regarding its use that continue to be debated today are: a) methods of determining candidacy for cisplatin use and b) strategies to mitigate the high incidence of nephrotoxicity observed. Given that the kidney clears majority of this drug (>90%), addressing both these issues requires an accurate estimation of renal function. Currently, patients are evaluated for cisplatin candidacy based on type of cancer, functional status and renal function. There is considerable heterogeneity across various oncology groups, institutions and countries with regards to the method used to determine renal function including serum creatinine (sCr), estimated creatinine clearance (eCrCl) by Cockcroft-Gault formula, and estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Measured creatinine clearance or glomerular filtration rate is preferable but is not employed routinely. CKD-EPI, despite using the same variables as the MDRD equation, reclassifies approximately 24.4% into a higher eGFR category and 0.6% into a lower eGFR category. For reasons displayed in table 1, it is the most widely used equation for eGFR amongst nephrologists. Its benefit of increased accuracy at GFR 60ml/min/1.73m^2 is an added advantage since the majority of patients receiving cisplatin would fall into that category. However, this method has not penetrated as deeply into the oncology practice where accurate estimation of renal function is essential to identify candidates best suited to receive drugs with a narrow therapeutic index. During the last year, we have assembled a database of over 6000 consecutive patients who received cisplatin at the Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH) and Dana-Farber Cancer Institute (DFCI) between 2005 and 2015. This database includes demographics, laboratory values, medical history, medication history and chemotherapy administered. Using these data, we propose the following aims:

	sCr	eCrCl (CG)	eGFR MDR D	eGFR (CKD
Demographics included	✖	✔	✔	✔
IDMS* standardized	✔	✖	✔	✔
Adjusted to BSA	✖	✖	✔	✔
Optimized for women	✖	✖	✔	✔
Accuracy at higher GFR(≥60ml/min/1.73 m^2)	N/A	N/A	✖	✔
Accuracy for predicting risk of mortality and ESRD	Low	Med	High	Highest
*IDMS: Isotope dilution mass spectrometry introduced in 2005 across the country				

Aim 1: To compare mortality and event-rates of cisplatin nephrotoxicity when eligibility for cisplatin use is determined by different methods to estimate pre-treatment kidney function. We hypothesize that an eGFR-based candidate selection using CKD-EPI will be superior

compared with eCrCl (by Cockcroft-Gault) and sCr at predicting nephrotoxicity and mortality amongst those receiving cisplatin. Patients will be divided into categories based on sCr (≤1.5mg/dl and >1.5mg/dl) eCrCl (≥60 ml/min or <60ml/min) and eGFR (≥60ml/min/1.73 m^2 or <60ml/min/1.73 m^2).

Aim 2: To develop and validate a clinically useful predictive model for cisplatin nephrotoxicity. We hypothesize that a model using readily available clinical and laboratory variables (including best kidney function measure from Aim 1) will be able to identify a large majority of patients at risk for nephrotoxicity amongst candidates for cisplatin chemotherapy and thus improve upon current standard using a single cutoff. To this end, we will: 1) Derive a predictive model using data from patients treated at DFCI and BWH (deelopment cohort). We will then validate this model in a separate set of patients treated at MGH (validation cohort) using AUC analysis.

Collectively, these studies will help provide foundation for a potential paradigm shift in the determination of cisplatin candidacy, and help tailor therapy by providing individualized risk estimates to patients in the office.

Research Strategy

SIGNIFICANCE

Overall cancer survival has improved to 67%[1] for all cancers and increasing emphasis is being placed on treatment with a tolerable toxicity profile while maintaining tumor eradication properties.[2] For instance, since its introduction in 1978, cisplatin has led to a dramatic survival advantage of patients with testicular, bladder, cervical, ovarian, lung, gastric, breast, head and neck cancers, malignant mesothelioma and some less-common tumors.[1,3] Taking testicular cancer as the example, introduction of cisplatin has led to patient survival of over 95%[3] and has added decades to patients' lives.[2] This success, however, has led to patients living longer often with effects of long-term toxicity and premature death. There is recent evidence that long-term circulating platinum levels are detectable in patients up to 20 years after treatment with cisplatin combination chemotherapy.[4] Renal function before and after cisplatin exposure is found to be a major determinant of long term circulating platinum which in turn is associated with hypercholesterolemia, hypertension, parasthesias and hypogonadism.[5] Therefore, there might be a link between short and long term nephrotoxicity and premature cardiovascular mortality. In addition, not only are acute kidney injury (AKI) and chronic kidney disease (CKD) independent risk factors for morbidity and mortality in the general population but a small study has recently found this to be the case in head and neck cancer patients receiving cisplatin.[6] One of the strategies of utmost importance to prevent late effects and premature mortality might be to attempt to decrease this nephrotoxicity in the short-term, by early recognition and prevention, which still continues to be observed in one-third of patients.[7-9] How might we reduce the nephrotoxicity? Our proposed strategy is to identify an improved method for evaluating candidacy for cisplatin use.

Comparison of measures of renal function:

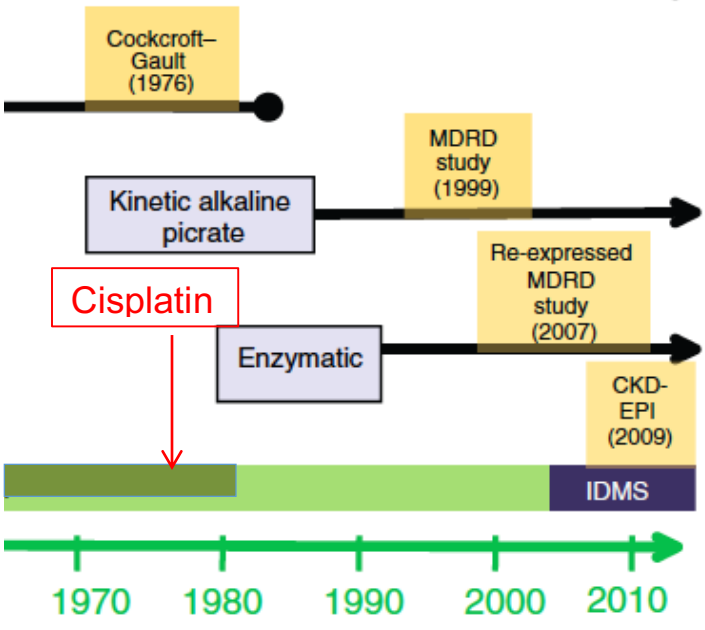

Figure 1: Adopted and modified from Stevens et al[10] timeline showing introduction of various measures of renal function relative to introduction of cisplatin in clinical practice.

Cisplatin is a known proximal tubular toxin that causes a dose-dependent drop in glomerular filtration rate (GFR).[8] Equations for estimating GFR have evolved since cisplatin was first employed in clinical practice and its drug dosing was determined, with most of the pharmacokinetic studies using the Cockcroft-Gault (CG) equation (see figure 1). It should be noted that the CG equation was developed from 249 white men with a mean estimated creatinine clearance (eCrCl) of 73 ml/min. In 1999, the Modification of Diet in Renal Disease (MDRD) study equation was derived from 1,628

men and women of black and white origin. The MDRD equation has been shown to be more accurate than CG.[10] Later in 2007, the National Kidney Disease Education Program (NKDEP) introduced the isotope dilution mass spectrometry (IDMS) reference standard to standardize creatinine assays across the country.[11] These standardized creatinine assays have improved the reliability, reproducibility and accuracy of measurement and have been adopted nationwide.[11] The MDRD equation[12] and the later developed higher accuracy Chronic Kidney Disease Epidemiology (CKD-EPI) equation was calibrated to include standardized creatinine assays, which could not be done for the CG equation due to unavailability of study samples from the original cohort. The CKD-EPI equation was developed using 12,150 subjects from diverse populations (8,254 for development and 3896 for validation).[13] One reason for improvement of the CKD-EPI equation over the MDRD was the inclusion of patients with and without chronic kidney disease (CKD) as opposed to the MDRD, which was developed using only CKD patients. This enabled a more accurate estimate of GFR over a wider range of values with better understanding of the complex relationship between creatinine and age, sex and race.[14] Thus, the CG equation, which continues to be employed in most oncology clinical trials for determining patient eligibility, is less accurate than the newer eGFR equations. Moreover, CG was not originally designed to be adjusted for body surface area; this lack of BSA adjustment could particularly be of concern in cancer patients owing to their low muscle mass.[10] Furthermore, the CKD-EPI equation offers increased precision over the MDRD for measuring glomerular filtration rate (GFR) $\geq$60 ml/min/1.73 m^2.[15] Since the majority of the patients receiving cisplatin would presumably fall into this category (i.e. eGFR $\geq$60 ml/min/1.73 m^2), the CKD-EPI would seem to be the preferred choice of all the equations available.[16] However, as a result of its relatively recent adoption in the nephrology literature and clinical practice, with apparent little penetration in non-nephrology specialties, there is scant evidence regarding its potential benefit.[14,17] Two groups have recently compared eCrCl and CKD-EPI in small studies with conflicting results. Tsao et al looked at 116 patients with urothelial cancer in a retrospective study and classified eligible vs ineligible patients using CG (with eCrCl <60 ml/min deemed ineligible) and CKD-EPI equations (with eGFR<60ml/min/1.73 m^2 deemed ineligible). They found that using CKD-EPI led to a relative 17% larger pool of eligible patients compared with CG, with an 87% concordance rate between the two equations.[18] A second study by Pal et al retrospectively evaluated 126 patients with bladder cancer and compared eligibility using CG, MDRD and CKD-EPI and found that the latter classified the least number of patients eligible for cisplatin.[19] However, neither of the studies included data on nephrotoxicity rates with the reclassification. Hence, there is need for better understanding of the impact of CKD-EPI for GFR estimation in a much larger number of patients not restricted to specific cancer types, age, race or kidney function.

The need for predictive modeling

In addition to determining the best method for estimating renal function, it would also be clinically useful to develop a predictive model that estimates risk of cisplatin nephrotoxicity similar to the Framingham risk score's prediction of cardiovascular disease.[20] This scoring system would enable identification of those individuals at high risk for nephrotoxicity and lead to consideration of appropriate steps for prevention, including use of alternative therapies. To date, there is limited understanding of risk factors for cisplatin nephrotoxicity. deJongh et al published a multivariable analysis of various types of toxicities in 400 patients who participated in Phase I/II clinical trials of two different cisplatin based regimens.[21] They reported a 7% rate of

nephrotoxicity (defined as ≥25% decline in creatinine clearance) that was associated with older age, female, smoking, hypoalbuminemia and paclitaxel co-administration on multivariable analysis. This study is not generalizable given the highly selected population of patients. Moreover, the rate of nephrotoxicity noted in the study is far lower than that reported in the literature, i.e. 7% vs 25-30%,[7-8,22] which may be explained by the uncommon definition of nephrotoxicity used in this study. In 2014, Kidera et al published a study of 401 inpatients receiving cisplatin as first-line chemotherapy and reported nephrotoxicity in 32% patients, when defined as a serum creatinine elevation of 1.5 to 3 times the upper limit of normal.[23] On multivariable analysis, they observed that non-steroidal anti-inflammatory drug use, hypomagnesemia and performance status were significantly associated with nephrotoxicity while age, sex and hypoalbuminemia were not. Concurrent chemotherapy and smoking status were not evaluated in this study. Neither of the studies evaluated baseline renal function or race, which are known risk factors for acute kidney injury.[21,23] Liu et al recently described a nephrotoxicity risk score that included genetic and non-genetic risk factors based only on 28 cases of nephrotoxicity amongst 116 patients, all with lung cancer.[24] Furthermore, this study did not include a validation cohort to evaluate the performance of their score. Hence, there is need for a larger study of patients exposed to cisplatin to be able to build a robust model with a better understanding of risk factors and a scoring system that is tested in one or more independent group of patients.

INNOVATION:

Our study is innovative because it ventures to change the paradigm of practice in oncology by re-evaluating cisplatin candidacy assessment that is based on renal function and risk factors for nephrotoxicity. Similar to the widely applicable Framingham risk score,[20] we aim to provide objectivity to risk assessment in the office using readily available clinical data. The lessons from the Framingham risk score application highlight the advantage of having a risk prediction model that considers that the presence of moderate-level of multiple risk factors may be more important than an isolated presence of one high-level risk factor. [20,25] Presentation of this data in the form of a score may also enhance the patient's understanding of their long-term risk and help them make an informed choice regarding their treatment options in consultation with their physician.

We also bring Nephrology expertise to this problem long tackled by Oncologists. We examine the use of the more accurate and precise CKD-EPI equation for estimation of GFR for cisplatin drug dosing. We will address this problem using data irrespective of cancer type (since demographics vary significantly by cancer type) and using a large study population to make the results generalizable. We have the opportunity to use data from two large data repositories, the Research Patient Data Repository (RPDR) from Partners HealthCare Hospitals and the Oncology Data Retrieval System (OncDRS) from the Dana Farber Cancer Institute. We have extensive prior experience with retrieving, programming and analyzing the wealth of data from these large data sources.

APPROACH:

AIM 1: To compare eligibility with mortality and incidence of cisplatin nephrotoxicity when baseline kidney function is estimated by different methods amongst patients who have received cisplatin. We hypothesize that an eGFR-based candidate selection by CKD-EPI

would be superior compared with eGFR by MDRD, estimated creatinine clearance (eCrCl) by Cockcroft-Gault and serum creatinine (sCr) at predicting nephrotoxicity and mortality amongst those receiving cisplatin. Patients will be divided into categories based on sCr (≤1.5mg/dl and >1.5mg/dl) eCrCl (≥60 ml/min or <60ml/min) and eGFR (≥60ml/min/1.73 m^2 or <60ml/min/1.73 m^2) by MDRD or CKD-EPI.

1.1: Inclusion and exclusion criteria:
Our inclusion and exclusion criteria for the two cohorts were as follows:
Inclusion criteria:

- Age ≥18 years of age
- Treated at DFCI main site, BWH or MGH between 2005 and 2015
- Patients having at least one baseline serum creatinine measurement within the pre-specified period of time (1 month) prior to initial cisplatin exposure and at least one creatinine measurement within 14 days after cisplatin exposure.

Exclusion criteria:

- Patients who had cisplatin administered in the setting of allergic desensitization

1.2 Assembly of the cohorts:
Cohort 1- Massachusetts General Hospital (MGH) data: After receiving Partners Institutional Review Board (IRB) approval, we requested the pharmacy research division at the MGH to provide a list of patients treated with the drug cisplatin over the past decade. This file included patients treated at MGH since the year 2005 reflecting the time that the pharmacy records were converted from paper to electronic to enable easier data retrieval. This file contained drug and dosing information as well as identifiable patient data including medical record numbers and dates of administration. Using the information obtained from pharmacy, we ran a query on the Partners RPDR, a data warehouse that collects clinical data from all Partners affiliated hospitals that provided us with corresponding data including demographics, medical history, laboratory values and medication history.

Cohort 2 - Brigham and Women's hospital (BWH) and the Dana Farber Cancer Institute (DFCI): The majority of the patients in this cohort receive cisplatin as an outpatient at DFCI. This data is collected into the OncDRS with pharmacy data incorporated into this repository. We have obtained data from the OncDRS system in addition to supplemental data from RPDR. Any missing data, erroneous or implausible values were cross-checked between the two databases and by chart review to ensure data integrity.

Mortality data: The RPDR and OncDRS systems collect mortality data from respective hospital administrative databases as well as the Social Security Death Master Index (SSDMI) that are updated monthly. The OncDRS, in addition, also collects death data from the cancer registry and National Death Index.

1.3 Definitions: Laboratory data was sorted according to the following definitions:
Baseline creatinine and additional labs: Labs resulted within 1 month prior to administration of the first date of the first course of cisplatin (referred to as index date henceforth) were included as the baseline. For patients with multiple lab values, those closest to the index date were chosen for inclusion. We also recorded serum magnesium and serum albumin to be included as

covariates for analysis. The baseline creatinine was chosen from the time closest index date because it will likely be the best reflection of renal function at the time of exposure to cisplatin. Peak BUN and creatinine: The highest value of creatinine within 14 days following the index date was chosen as the peak value. The rationale for choosing this timeline is that most nephrotoxicity is seen within 10-14 days of drug administration. Moreover, this is to best optimize the number of labs captured despite use of various intervals between cisplatin courses for patients included within the cohort (i.e. cisplatin administered every 2, 3 or 4 weeks). Nadir creatinine: Labs resulted within 1 month following the index date but occurring after the peak value was used to define the nadir. For patients with multiple lab results within this pre-specified time range, the results reflecting the lowest value of creatinine were chosen. Cisplatin-associated nephrotoxicity (CAN): We define CAN as a ≥0.3mg/dl rise in creatinine from baseline to peak measurements. This definition is adapted from the Acute kidney Injury Network (AKIN) criteria [27] which proposes the same degree of rise in creatinine over 48 hours to reflect kidney injury. However, based on our prelim data and routine oncology practice, most patients do not have a creatinine level re-checked within 48 hours of drug administration. Our definition is identical to stage I nephrotoxicity according to the National Cancer Institute's (NCI) nephrotoxicity criteria, which does not specify or restrict the number of hours over which acute kidney injury is observed. An additional distinct advantage of using NCI criteria is that they form the basis of majority of the literature in cisplatin nephrotoxicity and will help compare our study findings with the large body of published data.

Calculation of eGFR by CKD-EPI, MDRD and eCrCl by CG formulae:
We calculated the eGFR and CrCl as per standard formulae included below using the deemed baseline creatinine values and demographics at the time:

CKD-EPI GFR[13] = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] where: S_{cr} is serum creatinine in mg/dL,κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.
IDMS traceable MDRD eGFR[12] (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) x (1.212 if African American) *Conventional Units (creatinine as mg/dL; age in years)*
CG: eCrCl [26]= [((140-age) x weight)/(72 x S_{cr})] x 0.85 if female Where, eCrCl is expressed in mL/min, age is expressed in years, weight is expressed in kilograms, and S_{cr} is expressed in mg/dL

1.4: Statistical analysis: For aim 1, we will analyze the two cohorts combined. Number and percentages of patients who would have been eligible to receive the drug by applying four different criteria i.e. creatinine ≤1.5, creatinine clearance ≥60 ml/min, and eGFR (MDRD) ≥60 ml/min/1.73m^2 and CKD-EPI ≥60 ml/min/1.73m^2 will be calculated. Event rate of CAN and mortality will then be calculated in the entire cohort, and those eligible vs ineligible by each of the different criteria i.e, with creatinine ≤1.5 and creatinine >1.5, creatinine clearance ≥60

ml/min and <60ml/min as well as eGFR (MDRD and CKD-EPI) ≥60 ml/min/1.73m^2 and <60ml/min/1.73m^2. We will then use the paired McNemar tests in order to determine if there are statistically significant differences in the number of CAN detected by using the four renal function cutoffs mentioned above. All analyses will be carried out using SAS version 9.3.

1.5: Preliminary data:
During the last year, we requested data from RPDR and OncDRS repositories. This data has required extensive processing and programming to be included in the database and to align by dates with cisplatin exposure and to ensure data integrity. For cohort 1 (MGH), we received data on 2529 patients; after applying the above inclusion and exclusion criteria there were 2254 eligible patients. Similarly, for cohort 2 (BWH/DFCI), we received data on 5918 patients of which 4137 remained eligible.

AIM 2: To develop and validate a clinically useful predictive model for cisplatin nephrotoxicity. Our hypothesis is that a model using readily available clinical and laboratory variables including the best kidney function measure from Aim (1) will be able to identify patients at higher risk for nephrotoxicity amongst candidates for cisplatin chemotherapy and thus improve upon current methods of a single cutoff of creatinine or creatinine clearance. To this end, we will: 1) Derive a predictive model using data from patients treated at DFCI and BWH (development cohort). We will then test this model in an independent set of patients treated at MGH (validation cohort) using Area Under the Curve (AUC) analysis.

2.1: Test/development cohort: We will utilize the larger BWH/DFCI (cohort 2) as described above for initial development of the risk score. Important covariates including demographics (age, sex, race, height, weight at the time of initial cisplatin administration); history of diabetes, hypertension, pre-existing kidney disease (defined as chronic kidney disease with creatinine >1.5 or eGFR<60ml/min/1.73 m^2); cisplatin dose, dose frequency; baseline laboratory values including BUN, creatinine, magnesium, albumin; medication history with specific focus on use of diuretics, angiotensin converting enzyme inhibitors, amifostine, mannitol; as well as vital status will be collected. Missing data will be collected by chart review. CAN will be defined as described above in Aim #1.

2.2: Validation cohort: We will use the MGH (cohort 1) as the validation cohort. All data variables as described above for the development cohort will be included and analyzed.

2.3: Statistical analysis: For descriptive purposes, continuous variables will be compared by t-tests for normally distributed data and Wilcoxon/Kruskal Wallis tests for non-normally distributed data as appropriate. Categorical data will be compared using the chi-square test. Missing data will be handled by multiple imputation methods after completion of sensitivity analysis. We will carry out additional subgroup analysis on patients with creatinine >1.5 or eGFR by CKD-EPI <60ml/min/1.73 m^2. This will help us evaluate if there are any interactions or differing relationships between chronic kidney disease or pre-existing acute kidney injury as defined by these frequently used cutoffs and the exposure to cisplatin.

For developing the model using CAN yes/no as the binary primary outcome, we will first analyze all the variables with univariable logistic regression. Those that are significant on

univariate analysis will be entered into a multivariable logistic regression model with backward elimination to identify risk factors associated with the primary outcome. Those variables with p-value <0.05 will be retained in the final model. For each of the significant variables, quintiles of β coefficient that are not significantly different from each other will be grouped together. We will then divide the β coefficient of these collapsed categories by the smallest value of a β coefficient in the model to arrive at a score for every variable. The score will then be incorporated into the final model. We will assess the model's discrimination using the C-statistic and calibrate with the Hosmer-Lemeshow goodness-of-fit test using deciles. 95% confidence intervals will be calculated using nonparametric bootstrapping. We will proceed with external validation using the MGH cohort if the C-statistic is at least 0.70. Sensitivity, specificity, positive and negative predictive values will be calculated from both cohorts after selecting an appropriate score cutoff to distinguish low risk vs high risk for the primary outcome. In addition, a C statistic and H-L p-value will be calculated from the MGH cohort 2. All analyses will be carried out using SAS version 9.3.

LIMITATIONS AND POTENTIAL SOLUTIONS:

Serum creatinine continues to present an interesting limitation to any analysis given its limited sensitivity and specificity for identification of kidney injury. Despite this, we have chosen to identify cisplatin-associated nephrotoxicity using creatinine as our biomarker of choice as is also used by the NCI to define nephrotoxicity. Until newer biomarkers are widely adopted, accepted and translated into routine clinical practice, we believe this is a clinically relevant choice. This is especially the case, given our primary purpose of creating a risk-prediction model out of readily available clinical and laboratory variables. Second, we have defined cisplatin-associated nephrotoxicity without pathological confirmation. However, a kidney biopsy for tissue-based confirmation is rarely performed in this clinical setting, hence this would not be a major change from routine clinical practice. Moreover, if significant rise in creatinine is observed within the nephrotoxicity time frame, then the clinical practice algorithm (i.e. delaying further chemotherapy or discontinuing cisplatin) would likely be no different regardless of the etiology. Lastly, this study may also be limited by the fact that the risk prediction model development, internal validation and external validation are performed in a tertiary care setting. However, these hospitals have a completely separate and independent practice. Our attempts in future years would be to further validate the risk score generated from this study in community settings.

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